DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
NTP Interagency Center for the
Evaluation of Alternative Toxicological
Methods
P. O. Box 12233
Research Triangle Park, NC 27709

February 28, 2008

The Honorable Andrew C. von Eschenbach, M.D.
Commissioner of Food and Drugs
U.S. Food and Drug Administration
Parklawn Building, Room 1471
5600 Fishers Lane
Rockville, Maryland 20892

Dear Dr. von Eschenbach:

I am pleased to forward toxicological test method recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for your consideration. These test method recommendations are being sent to you for action pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*-3).

Two *in vitro* alternative test methods are recommended for estimating starting doses for acute oral systemic toxicity tests. Detailed recommendations are provided in the report, *The Interagency Coordinating Committee on the Validation of Alternative Methods Test Method Evaluation Report: In Vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests* (NIH Publication No. 07-4519, Enclosure 1).

ICCVAM recommends that the test methods should be considered before using animals for acute oral toxicity testing, and that the methods should be used where determined appropriate. Data from the test methods should be used in a weight-of-evidence approach for determining starting doses for *in vivo* studies. Using these *in vitro* methods where appropriate is expected to reduce the number of animals required for each toxicity test. ICCVAM concluded that the *in vitro* test methods are not sufficiently accurate to replace animals for regulatory hazard classification purposes.

The report also provides recommendations for: (1) standardized protocols that should be used when performing the *in vitro* test methods, (2) future studies to improve the usefulness of *in vitro* assays for assessing acute oral systemic toxicity for regulatory hazard classification purposes, and (3) performance standards that can be used to assess the performance of similar cytotoxicity test methods. The report includes technical summaries for the two *in vitro* basal cytotoxicity test methods, applicable U.S. Federal regulations and testing guidelines for acute

oral systemic toxicity, relevant *Federal Register* notices, the scientific peer review panel report, and discussion of public comments received during the evaluation. ICCVAM initially reviewed the status of *in vitro* methods for estimating acute oral systemic toxicity at an international workshop in October 2000. Based on workshop deliberations, ICCVAM recommended that data from *in vitro* cytotoxicity methods should be considered as one of the tools for setting starting doses for acute toxicity studies, and that this approach could potentially reduce the total number of animals required for each study. ICCVAM transmitted this and other related recommendations to Federal agencies in March 2003.

NICEATM, in collaboration with the European Centre for the Validation of Alternative Methods (ECVAM), subsequently designed and conducted an independent international validation study to further characterize the usefulness and limitations of two *in vitro* cytotoxicity test methods proposed for estimating starting doses for rodent acute oral systemic toxicity tests. The validation study results and analyses are described in a comprehensive Background Review Document (Enclosure 2) and support the ICCVAM recommendations.

Pursuant to Sections 4(a) and 4(d) of the ICCVAM Authorization Act, agencies are required to review ICCVAM test method recommendations and notify the ICCVAM in writing of their findings, including identification of relevant test methods for which the ICCVAM test recommendations may be added or substituted, no later than 180 days after receipt of the recommendations. Therefore, I would ask that you please send your agency's response by August 28, 2008, to Rear Admiral William S. Stokes, Executive Director, ICCVAM, NIEHS, P.O. Box 12233, Mail Code EC-17, Research Triangle Park, NC 27709, Phone: 919-541-7997, Fax: 919-541-0947, Email: *stokes@niehs.nih.gov*. ICCVAM is required to make final ICCVAM test method recommendations and the responses from agencies regarding such recommendations available to the public per Section 3(e)(6) of the Act. Accordingly, your response will be posted on the NICEATM-ICCVAM website at *http://iccvam.niehs.nih.gov*.

I appreciate your agency's participation on ICCVAM. The committee serves an important role in facilitating the scientific evaluation and adoption of test methods that will help protect human health and the environment while providing for improved animal welfare whenever possible.

Sincerely,

/s/

Samuel H. Wilson
Acting Director

Enclosures

cc:
Suzanne Fitzpatrick, Ph.D., FDA ICCVAM Principal Agency Representative